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## Chapter 24

# Tetracyclines and Chloramphenicol

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## TETRACYCLINES

All the tetracyclines are primarily bacteriostatic at therapeutic concentrations and have a broad spectrum that includes gram-positive, gram-negative, aerobic, and anaerobic bacteria, spirochetes, mycoplasmas, rickettsiae, chlamydiae, and some protozoans. The analogues can be divided into three groups based on differences in their pharmacology: (1) the short-acting compounds chlortetracycline, oxytetracycline, and tetracycline; (2) an intermediate group consisting of demeclocycline and methacycline; and (3) the more recently discovered, longer-acting compounds doxycycline and minocycline. Although several other derivatives have been developed called *glycylcyclines*, which have activity against tetracycline-resistant bacteria, none are available at this time.<sup>1</sup>

## Structure, Derivation, Nomenclature, and Brand Names

Unlike the fortuitous discovery of penicillin by Fleming, the first tetracycline, chlortetracycline, was discovered by screening organisms obtained from the soil for their antimicrobial properties. Benjamin M. Duggar, a meticulous mycologist in his seventies, noted unusual antimicrobial activity from organisms that formed a golden yellow colony.<sup>2</sup> He designated the organism *Streptomyces aureofaciens* (L. *aurum*, "golden") and named the product *Aureomycin*. Oxytetracycline was derived from *Streptomyces rimosus* in 1950, and tetracycline was produced by the catalytic dehalogenation of chlortetracycline in 1953. The two long-acting compounds were derived semisynthetically: doxycycline in 1966 and minocycline in 1967.

major brand names, doses, and costs are listed in Table 24-1. Of these, tetracycline HCl and doxycycline have emerged as the most useful clinically. Chlortetracycline (Aureomycin), the first member of the family, is no longer available except for topical use, and methacycline (Rondomycin) has been withdrawn from the market.

## Mechanism of Action

The tetracyclines enter bacteria by passive diffusion through porins in gram-negative bacteria and are probably accumulated by a  $\Delta pH$ -dependent process.<sup>1-4</sup> Once within the cell, they reversibly bind primarily to the 30S ribosomal subunit at a position that blocks the binding of the aminoacyl-transfer RNA to the acceptor site on the messenger RNA-ribosome complex.<sup>5</sup> This prevents the addition of new amino acids into the growing peptide chain. The tetracyclines also inhibit protein synthesis in mammalian cells, particularly in mitochondrial ribosomes, but apparently are not in sufficient concentration in these structures to produce severe toxicity.<sup>6</sup>

## In Vitro Activity

The antimicrobial spectra of all the tetracyclines are almost identical. Some differences, however, in the degree of activity against these organisms do exist among the analogues. In general, the lipophilic congeners are more active than those that are more hydrophilic. It follows, therefore, that minocycline is the most active of the analogues, closely followed by doxycycline. The minimal inhibitory concentration of the more hydrophilic congeners oxytetracycline and tetracycline are two- to fourfold higher against many bacteria and are the least-active analogues. Despite these differences, for cost reasons it is recommended that tetracycline be used in the clinical microbiology laboratory to evaluate susceptibility for all the analogues.<sup>7</sup> Minimal inhibitory concentrations of tetracycline and doxycycline for many aerobic bacteria are given in Table 24-2. For the

TABLE 24-1 The Names, Preparations, and Usual Adult Oral Dosages for the Tetracyclines Currently Available in the United States

| Generic Name (Major Brand Name, Company)* | Oral Preparations                                                                                                   | Usual Adult Oral Dosage                                |
|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Short-acting</b>                       |                                                                                                                     |                                                        |
| Oxytetracycline (Terramycin Pfizer)       | Capsules 125, 250 mg                                                                                                | 500 mg q6h                                             |
| Tetracycline HCl†                         | Capsules 100, 250, 500 mg<br>Syrup 125 mg/5 ml                                                                      | 500 mg q6h                                             |
| <b>Intermediate</b>                       |                                                                                                                     |                                                        |
| Demeclocycline HCl (Declomycin, Lederle)  | Capsules 150 mg<br>Tablets 150, 300 mg                                                                              | 300 mg q12h                                            |
| <b>Long-acting§</b>                       |                                                                                                                     |                                                        |
| Doxycycline (Vibramycin Pfizer)           | Capsules (hydrate) 50, 100 mg<br>Tablets 50, 100 mg<br>Syrup (calcium) 50 mg/5 ml<br>Syrup (monohydrate) 25 mg/5 ml | 200 mg (or 100 mg q12h for first day) then 100 mg q24h |
| Minocycline (Minocin Lederle)             | Capsules and tablets 50, 100 mg<br>Suspension 50 mg/5 ml                                                            | 200 mg then 100 mg q12h                                |

\*Many other brands are available for some of the analogues.

†The short-acting tetracyclines are also available for intravenous administration at usual doses of 500 mg every 6 to 12 hours not to exceed 2 g daily. However, most prefer doxycycline for this route of administration. Preparation combined with a local anesthetic agent can be given intramuscularly, but these are not recommended.

‡Tetracycline is also available as a tetracycline phosphate complex (Tetrex, Bristol) intended to

# TETRACYCLINE

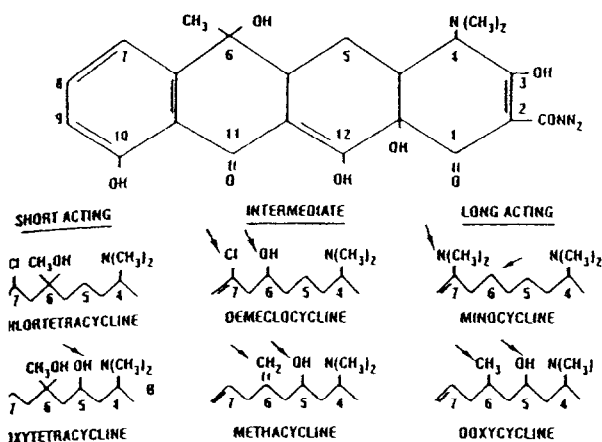


FIG. 24-1. Chemical structure of the tetracyclines. The analogues from tetracycline at the fifth, sixth, or seventh position, as indicated by arrows.

ities of the other analogues, the reader is referred to the extensive work from the laboratory of Finland and colleagues.<sup>8-10</sup> Although many of the aerobic and facultative anaerobic organisms are within the spectrum of the tetracyclines, more effective ones are available for the treatment of infections caused by most of these bacteria. Pneumococci and *Haemophilus influenzae* can be treated by concentrations of tetracyclines achieved in the serum; this provides a rationale for their use in sinusitis and acute exacerbations of chronic bronchitis.<sup>11</sup> However, pneumococci resis-

tant to penicillin are generally more resistant to tetracyclines, although doxycycline is the more active congener.<sup>12-14</sup> Gonococci and meningococci are extremely susceptible; unfortunately, gonococci resistant to penicillin G also tend to be resistant to tetracycline.<sup>14, 15</sup> In most cases, *Escherichia coli* acquired outside the hospital setting can be inhibited by concentrations achieved in the urine, if not the serum. Tetracyclines, therefore, are useful agents for the treatment of acute, uncomplicated, urinary tract infections and the acute urethral syndrome. *Pseudomonas pseudomallei* organisms are generally sensitive, and this has therapeutic importance, as does the high degree of susceptibility of *Brucella* spp.<sup>16, 17</sup> *Vibrio cholerae*, *Vibrio vulnificus*, and other vibrios are generally susceptible, and the tetracyclines are important for therapy for diseases caused by this group of organisms.<sup>18</sup> Although *Campylobacter* spp. are generally susceptible, a high percentage of resistant isolates has been noted in some countries.<sup>19-21</sup> Therefore, it is not the drug of choice for infections caused by these bacteria. *Shigella* organisms have become increasingly resistant.<sup>22</sup> *Mycobacterium marinum* is susceptible and appears to respond clinically.<sup>23</sup>

The tetracyclines have activity against many anaerobic organisms (Table 24-3).<sup>24</sup> Their activity against *Actinomyces* is particularly relevant clinically. Doxycycline is more active against *Bacteroides fragilis* than tetracycline is, but other agents are preferred for infections caused by this organism. The activity of the tetracyclines against anaerobic bacteria, however, may be partially responsible for the effectiveness of the neomycin-tetracycline combination and doxycycline alone as alternative oral presurgical bowel preparations.<sup>25, 26</sup> Many pathogenic spirochetes are susceptible, including *Borrelia burgdorferi*, the agent of Lyme disease.<sup>27</sup> Other organisms generally inhibited by this group of antibiotics include rickettsiae, chlamydiae, mycoplasmas, and, to a limited degree, protozoans (*Plasmodium* spp. and *Entamoeba histolytica*).<sup>28</sup>

Bacteria develop resistance to the tetracyclines predominantly by

TABLE 24-2. Minimal Inhibitory Concentration of Tetracycline and Doxycycline for Common Aerobic and Facultative Anaerobic Bacteria

| Organism                           | No. of Strains | Antibiotic   | Cumulative Percentage Inhibited by Indicated Concentrations (μg/ml) |     |     |     |     |
|------------------------------------|----------------|--------------|---------------------------------------------------------------------|-----|-----|-----|-----|
|                                    |                |              | 0.4                                                                 | 0.8 | 1.6 | 3.2 | 6.4 |
| positive                           |                |              |                                                                     |     |     |     |     |
| <i>Staphylococcus aureus</i>       | 56             | Tetracycline | 0                                                                   | 2   | 20  | 65  | 67  |
|                                    |                | Doxycycline  | 2                                                                   | 25  | 63  | 65  | 68  |
| <i>Staphylococcus pyogenes</i> *   | 63             | Tetracycline | 10                                                                  | 50  | 80  | 87  | 90  |
|                                    |                | Doxycycline  | 56                                                                  | 90  | 90  | 95  | 95  |
| <i>Staphylococcus pneumoniae</i> † | 35             | Tetracycline | 70                                                                  | 96  | 96  | 100 | —   |
|                                    |                | Doxycycline  | 100                                                                 | —   | —   | —   | —   |
| <i>Staphylococcus streptococci</i> | 12             | Tetracycline | 0                                                                   | 0   | 50  | 50  | 50  |
|                                    |                | Doxycycline  | 0                                                                   | 50  | 50  | 50  | 50  |
| <i>Staphylococcus</i>              | 36             | Tetracycline | 0                                                                   | 0   | 0   | 0   | 10  |
|                                    |                | Doxycycline  | 0                                                                   | 0   | 0   | 0   | 10  |
| negative‡                          |                |              |                                                                     |     |     |     |     |
| <i>Neisseria gonorrhoeae</i> §     | 25             | Tetracycline | 5                                                                   | 60  | 85  | 88  | 100 |
|                                    |                | Doxycycline  | 60                                                                  | 75  | 80  | 92  | 100 |
| <i>Neisseria meningitidis</i>      | 10             | Tetracycline | 0                                                                   | 50  | —   | 100 | —   |
|                                    |                | Doxycycline  | 0                                                                   | —   | 50  | —   | 100 |
| <i>Haemophilus influenzae</i>      | 15             | Tetracycline | 0                                                                   | 0   | 0   | 33  | 87  |
|                                    |                | Doxycycline  | 0                                                                   | 0   | 60  | 93  | 100 |
| <i>Escherichia coli</i>            | 48             | Tetracycline | 0                                                                   | 0   | 0   | 5   | 35  |
|                                    |                | Doxycycline  | 0                                                                   | 0   | 0   | 5   | 35  |
| <i>Mycobacterium pneumoniae</i>    | 17             | Tetracycline | 0                                                                   | 0   | 0   | 0   | 5   |
|                                    |                | Doxycycline  | 0                                                                   | 0   | 0   | 0   | 12  |
| <i>Mycobacter</i> spp              | 10             | Tetracycline | 0                                                                   | 10  | 30  | 50  | 70  |
|                                    |                | Doxycycline  | 0                                                                   | 0   | 0   | 0   | 10  |
| <i>Pseudomonas pseudomallei</i>    | 10             | Tetracycline | 0                                                                   | 0   | 60  | 100 | —   |
| <i>Campylobacter jejuni</i>        | 172            | Tetracycline | 44                                                                  | 62  | 74  | 81  | 84  |
|                                    | 107            | Doxycycline  | 68                                                                  | 74  | 79  | 80  | 86  |
| <i>Shigella</i> spp                | 213            | Tetracycline | 0                                                                   | 10  | 12  | 50  | 50  |

\*Recent series indicate that 30 to 40% of *Strep. pyogenes* have become resistant to the tetracyclines.  
 †Tetracycline-resistant *Strep. pneumoniae* strains are more common in some areas. Those strains resistant to penicillin tend to be resistant to the tetracyclines.  
 ‡*Neisseria meningitidis* (indole positive), *Proteus* spp., and *P. aeruginosa* are generally resistant to 25 μg/ml.  
 §*Staphylococcus aureus* resistant to penicillin G also tend to be resistant to tetracycline.

Minimal inhibitory concentration of minocycline for meningococci is 1.6 μg/ml (range 0.3 to 1.6 μg/ml).

\*8-10, 16-19, 22. Organisms should be considered susceptible if the minimal inhibitory concentrations are 4 μg/ml or less. A moderate susceptibility range of up to 8 μg/ml may be useful for the urinary tract infection.

TABLE 24-3 Minimal Inhibitory Concentrations of Tetracycline and Doxycycline for Common Anaerobic Bacteria\*

| Organism                                           | No. of Strains | Antibiotic   | Cumulative Percentage Susceptible to Indicated Concentration ( $\mu\text{g/ml}$ ) |     |     |     |     |
|----------------------------------------------------|----------------|--------------|-----------------------------------------------------------------------------------|-----|-----|-----|-----|
|                                                    |                |              | 0.5                                                                               | 1.0 | 2.0 | 4.0 | 8.0 |
| Gram-positive                                      |                |              |                                                                                   |     |     |     |     |
| <i>Peptococcus</i>                                 | 59             | Tetracycline | 25                                                                                | 29  | 36  | 36  | 37  |
| <i>Peptostreptococcus</i>                          | 29             | Tetracycline | 38                                                                                | 41  | 48  | 52  | 72  |
|                                                    |                | Doxycycline  | 45                                                                                | 45  | 66  | 79  | 97  |
| <i>Streptococci, anaerobic and microaerophilic</i> | 10             | Tetracycline | 50                                                                                | 60  | 70  | 90  | 90  |
|                                                    |                | Doxycycline  | 70                                                                                | 90  | 90  | 90  | 100 |
| <i>Eubacterium</i>                                 | 17             | Tetracycline | 24                                                                                | 59  | 65  | 65  | 77  |
|                                                    |                | Doxycycline  | 59                                                                                | 65  | 77  | 82  | 88  |
| <i>Propionibacterium</i>                           | 12             | Tetracycline | 58                                                                                | 75  | 83  | 83  | 83  |
|                                                    |                | Doxycycline  | 75                                                                                | 83  | 83  | 92  | 92  |
| <i>Clostridium perfringens</i>                     | 9              | Tetracycline | 22                                                                                | 22  | 56  | 67  | 67  |
|                                                    |                | Doxycycline  | 67                                                                                | 67  | 67  | 78  | 89  |
| Other clostridia                                   | 33             | Tetracycline | 36                                                                                | 46  | 49  | 52  | 61  |
|                                                    |                | Doxycycline  | 49                                                                                | 52  | 61  | 68  | 82  |
| <i>Actinomyces</i>                                 | 16             | Tetracycline | 56                                                                                | 69  | 94  | 94  | 94  |
|                                                    |                | Doxycycline  | 63                                                                                | 69  | 94  | 100 | —   |
| Gram-negative                                      |                |              |                                                                                   |     |     |     |     |
| Gram-negative cocci                                | 26             | Tetracycline | 54                                                                                | 69  | 73  | 73  | 73  |
|                                                    |                | Doxycycline  | 58                                                                                | 69  | 73  | 81  | 96  |
| <i>Fusobacterium</i>                               | 34             | Tetracycline | 94                                                                                | 97  | 97  | 97  | 97  |
|                                                    |                | Doxycycline  | 94                                                                                | 94  | 94  | 94  | 100 |
| <i>Bacteroides fragilis</i>                        | 76             | Tetracycline | 25                                                                                | 40  | 40  | 42  | 46  |
|                                                    |                | Doxycycline  | 41                                                                                | 42  | 50  | 75  | 88  |
| <i>Prevotella melaninogenica</i>                   | 67             | Tetracycline | 75                                                                                | 76  | 79  | 87  | 94  |
|                                                    |                | Doxycycline  | 75                                                                                | 78  | 90  | 96  | 97  |
| Other <i>Bacteroides</i> spp                       | 72             | Tetracycline | 33                                                                                | 35  | 43  | 50  | 60  |
| <i>Selenomonas</i>                                 |                | Doxycycline  | 40                                                                                | 43  | 53  | 68  | 79  |

\*An organism with a minimal inhibitory concentration of 4  $\mu\text{g/ml}$  or less should be considered susceptible.

Modified from Sutter VL, Finegold SM. Susceptibility of anaerobic bacteria to 23 antimicrobial agents. *Antimicrob Agents Chemother* 1976;10:736.

preventing the accumulation of tetracycline within the cell. This is accomplished by decreasing the influx or increasing the ability of the cell to export the antibiotic.<sup>4-10</sup> Rarely, the tetracyclines are inactivated biologically or altered chemically by resistant bacteria; oxidative destruction has been found in a few species.<sup>29-35</sup> Resistance to one tetracycline usually implies resistance to all, although there are marked differences in the degree of resistance among species. The resistance among bacteria can be mediated by transferable resistance plasmids. The tetracyclines have been widely used in feeds to promote growth in animals. This may be a major factor in providing selective antibiotic pressure for the spread of plasmid-mediated resistance to these and other antibiotics.<sup>16-18</sup>

## Pharmacology

Serum levels achieved by usual oral doses in adults are given in Figure 24-2. Absorption occurs primarily in the proximal small bowel and produces peak serum concentrations 1 to 3 hours after administration. The commonly used 500-mg therapeutic dose of tetracycline gives a serum level of 4  $\mu\text{g/ml}$ , the highest of all the short-acting analogues.<sup>39</sup> Doxycycline and minocycline (200 mg) achieve serum levels of about 2.5  $\mu\text{g/ml}$ , slightly higher than levels attained by the larger therapeutic doses of the intermediate agents.<sup>40-44</sup>

After the intravenous administration of 500 mg, serum levels of the short-acting agents (not shown) are approximately 8  $\mu\text{g/ml}$  at 30 minutes and decrease to 2 to 3  $\mu\text{g/ml}$  by 5 hours.<sup>45</sup> Intravenous injection of the usual 200-mg loading dose of the long-acting agents doxycycline and minocycline produces serum levels of approximately 4  $\mu\text{g/ml}$  at 30 minutes. Once tissue distribution occurs for the long-acting analogues, the levels are almost identical to the concentrations achieved orally.<sup>40-46</sup> Thrombophlebitis is a frequent complication of the intravenous preparations. Intramuscular preparations are available for the short-acting compounds but are not recommended because of the severe pain produced on injection, even when they are mixed with local anesthetic.

compared in Table 24-4. The high levels obtained orally with tetracycline compared with other short-acting agents are due primarily to better absorption from the gastrointestinal tract. The long-acting analogues doxycycline and minocycline are absorbed almost completely; thus, high serum levels are achieved with relatively small doses.<sup>40-41</sup> The tetracyclines can be differentiated into three groups on the basis of their different half-lives. Doxycycline has the longest of all and allows therapeutic levels to be maintained with a single

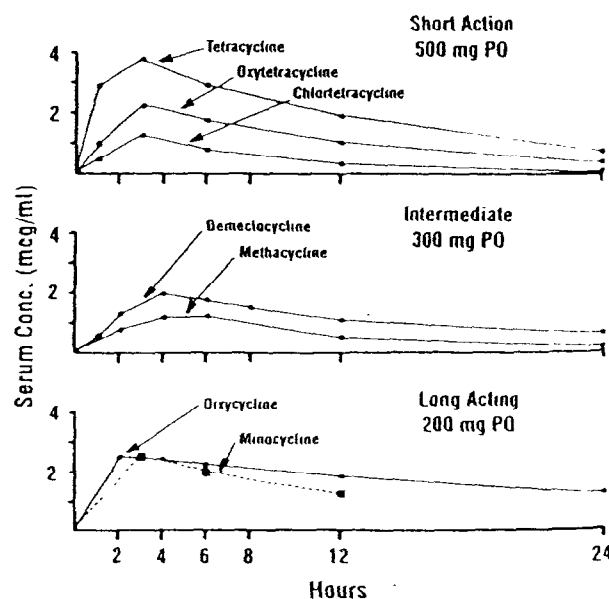


FIGURE 24-2. Serum levels achieved with the usually recommended oral doses of the tetracyclines. Chlortetracycline and methacycline are no

TABLE 24-4 Pharmacokinetic Features of the Tetracyclines\*

| Antibiotic      | Gastrointestinal Absorption (%) | Half-Life (h) | Renal Clearance† (ml/min/1.73 m <sup>2</sup> ) | Urinary Recovery (%) | Apparent Volume of Distribution‡ (Liters) | Protein Binding‡ (%) |
|-----------------|---------------------------------|---------------|------------------------------------------------|----------------------|-------------------------------------------|----------------------|
| Short-acting    |                                 |               |                                                |                      |                                           |                      |
| Oxytetracycline | 58                              | 9             | 99                                             | 70                   | 128                                       | 35                   |
| Tetracycline    | 77                              | 8             | 74                                             | 60                   | 108                                       | 65                   |
| Intermediate    |                                 |               |                                                |                      |                                           |                      |
| Demeclocycline  | 66                              | 12            | 35                                             | 39                   | 121                                       | 91                   |
| Methacycline    | 58                              | 14            | 31                                             | 60                   | 79                                        | 90                   |
| Long-acting     |                                 |               |                                                |                      |                                           |                      |
| Doxycycline     | 93                              | 18            | 10                                             | 42                   | 50                                        | 93                   |
| Minocycline     | 95                              | 16            | 9                                              | 6                    | 60                                        | 76                   |

\*The pharmacokinetic values vary considerably from laboratory to laboratory. These values were selected in most instances because comparative data were available from reliable investigators.

†After single-dose intravenous administration.

‡Ultrafiltration technique.

Data from refs. 40-45 and 45-48.

daily dose, although twice-daily regimens are frequently recommended.<sup>40</sup> The 8-hour half-life of tetracycline suggests that the dosage interval could be 8 hours for this antibiotic when it is used to treat minor infections.<sup>45</sup> The half-lives of the compounds are determined mainly by the rate of excretion by the kidneys. Chlortetracycline is an exception: it has a short half-life despite a slow rate of clearance as a result of the marked instability of the compound *in vitro* as well as *in vivo*.<sup>45</sup> Adequate therapeutic concentrations of all the tetracyclines, with the possible exception of chlortetracycline and minocycline, are achieved in the urine for the treatment of urinary tract infections caused by sensitive organisms. The degree of protein binding of the analogues is variable, depending on the methods used for the determination, but it tends to be greater for the intermediate- and long-acting compounds.<sup>46-48</sup> This may be one of the factors that determines their slow rate of renal excretion. The apparent volume of distribution for most of the tetracyclines is greater than that of intracellular body water, thus indicating sequestration in tissues, presumably the liver.<sup>45</sup> Minocycline and doxycycline have the smallest volume of distribution, another factor that tends to enhance their serum levels.<sup>46</sup>

### Tissue Distribution

The tetracyclines can be found in small amounts in many tissues and fluids, including the lung, liver, kidney, brain, sputum, and mucosal fluid. For tetracycline, the levels in the cerebral spinal fluid are approximately 10 to 26% of the serum levels,<sup>49-50</sup> whereas concentrations in synovial fluid and the maxillary sinus mucosa approach serum levels.<sup>51, 52</sup> All the tetracyclines are concentrated in unobstructed bile and produce levels in this fluid 5 to 20 times those obtained in the serum. It has been suggested that lipid solubility is a primary determinant for the diffusion in many tissues. Minocycline, followed by doxycycline, is more lipophilic at a physiologic pH than are the other drugs. This may explain why minocycline reaches sufficient concentrations in saliva and tears to eradicate the meningococcal carrier state, whereas the other tetracyclines do not.<sup>53-54</sup> The tetracyclines cross the placenta and accumulate in fetal bone and teeth and therefore should not be given during pregnancy.<sup>55-56</sup> They are excreted in breast milk; however, concentrations in the infant's serum are below detectability.<sup>57</sup>

### Renal and Hepatic Insufficiency

The tetracyclines should not be used in patients with renal failure. Doxycycline, the only exception, is excreted in the gastrointestinal tract under these circumstances. Neither the half-life nor the therapeutic dose of this antibiotic varies with alterations in renal function.<sup>54</sup> The tetracyclines are slowly removed by hemodialysis but not effectively by peritoneal dialysis. Hepatic disease is not known to

cause elevated serum levels of the tetracyclines. However, they should be used very cautiously in such situations, because they have been noted to cause hepatic toxicity.

### Assay

The tetracyclines can be measured by a number of different techniques. These include bioassay using *Bacillus cereus* as the test organism, by high-performance liquid chromatographic procedures, or by direct fluorescent chemical analysis,<sup>59-61</sup> but monitoring of serum levels during therapy is rarely indicated.

### Toxicity

#### Skin and Allergy

Hypersensitivity reactions including anaphylaxis, urticaria, periorbital edema, fixed drug eruptions, and morbilliform rashes occur with tetracyclines but are not common.<sup>62-64</sup> A patient who is allergic to one analogue should be considered to be allergic to all. There are a number of recent reports of a systemic lupus erythematosus-like syndrome reported in association with minocycline. These patients have antinuclear antibody. Symptoms disappear in most patients when the antibiotic is discontinued and recur when rechallenged.<sup>65-67</sup> Photosensitivity reactions consisting of a red rash on areas exposed to sunlight that is frequently associated with onycholysis are most common in patients receiving demeclocycline but occur with all analogues.<sup>68, 69</sup> They appear to be a toxic rather than an allergic reaction. Prolonged administration of minocycline has been noted rarely to cause nail, skin, and scleral pigmentation, which is usually reversible, as well as an asymptomatic black pigmentation of the thyroid.<sup>70-71</sup> A blue or blue-black discoloration of the gums also has been reported; this appears to be secondary to bone pigmentation, which is visible through the oral mucosal tissues. The pigmentation is permanent.<sup>72, 73</sup>

#### Teeth and Bones

A gray-brown to yellow discoloration of the teeth has been noted in some communities in 80% of the children taking tetracyclines.<sup>74</sup> This side effect is permanent and may be associated with hypoplasia of the enamel<sup>64, 75</sup> and depression of skeletal growth in premature infants.<sup>76</sup> The darkening effect of tetracyclines on permanent teeth appears to be related to the total dose of the antibiotic administered. In a retrospective study, cosmetically noticeable but mild darkening of the permanent teeth occurred in 3 of 14 children receiving five courses of tetracycline, whereas 4 of 6 children receiving eight courses had moderate darkening of the enamel.<sup>77</sup> Primary teeth generally show more darkening than do the larger, thicker, and more opaque permanent teeth. Since there is some variability in staining

with similar tetracycline exposure, it is prudent not to administer these agents to pregnant women and to children up to the age of 8 years, the period when tooth enamel is being formed. For this reason, the Food and Drug Administration has withdrawn from the market the concentrated liquid dosage forms (drops) specifically intended for pediatric use.<sup>78</sup> It is not unreasonable, however, to administer a single course of tetracycline therapy to young children for specifically defined indications when the alternative regime may produce more severe toxicity. Thus, the tetracyclines may be indicated for children suspected of having Rocky Mountain spotted fever who can tolerate oral medications. Doxycycline binds less with calcium than do other tetracyclines and may cause dental changes less frequently in children.<sup>79</sup>

### Gastrointestinal Symptoms

The tetracyclines are irritative substances and frequently produce gastrointestinal symptoms after oral administration. Esophageal ulcerations that are manifested as retrosternal pain exacerbated by swallowing have been clearly documented after tetracycline and doxycycline administration. In most cases, the patients were taking the capsules with little or no fluid just before going to bed. A word of caution to the patient is indicated in order to prevent this toxicity. The complication may also occur in patients with esophageal obstruction or motility disorders.<sup>80, 81</sup> Nausea, vomiting, and epigastric distress are dose related and limit the dose of most of the analogues. The administration of food with doxycycline, minocycline, or oxytetracycline may ameliorate some of these symptoms, but food seriously decreases the absorption of the other tetracyclines. Diarrhea is most often associated with analogues that are poorly absorbed and appears to be related to alterations in the enteric flora. Doxycycline produces less of an effect on bowel flora than does tetracycline.<sup>82</sup> The diarrhea usually subsides when treatment with the antibiotic is stopped, but prolonged symptoms due to pseudomembranous colitis have been reported.<sup>83</sup> Tetracycline also has been noted, rarely, to cause pancreatitis with or without overt liver disease.<sup>84</sup>

### Liver

The hepatotoxicity of the tetracyclines, first described in patients receiving intravenous chlortetracycline but now described with other analogues, appears pathologically as a fine droplet fatty metamorphosis and results in a high mortality.<sup>85, 86</sup> The administration of less than 2 g/day intravenously is not associated with liver dysfunction or injury except in pregnant women, who are particularly at risk,<sup>87</sup> and in patients with an excessive serum level due to renal failure.<sup>88</sup> This toxicity is rarely reported with doxycycline.<sup>89, 90</sup>

### Renal Function

The tetracyclines aggravate preexisting renal failure by inhibiting protein synthesis, which increases the azotemia from amino acid metabolism.<sup>91</sup> Nephrogenic diabetes insipidus is produced by demeclocycline, a side effect that has been used therapeutically to reverse chronic inappropriate antidiuretic hormone secretion;<sup>92</sup> renal failure has complicated its use for this purpose in patients with cirrhosis.<sup>93</sup> Outdated tetracycline has produced a reversible Fanconi-like syndrome with renal tubular acidosis, but tetracycline formulations producing this syndrome have been modified. It is unlikely that this complication will recur.<sup>94</sup>

### Nervous and Sensory Systems

Vertigo is a side effect unique to minocycline. Symptoms of light-

reversible within several days after the discontinuation of therapy with the antibiotic, but this side effect has seriously limited the use of minocycline.<sup>95</sup> Benign intracranial hypertension (pseudotumor cerebri) has been described in infants and adults with many of the analogues.<sup>96, 98</sup>

### Superinfection

Colonization by tetracycline-resistant organisms is a frequent occurrence during tetracycline therapy and is generally of little clinical significance. Rarely, a fulminating diarrhea resulting from *Clostridium difficile* pseudomembranous colitis or staphylococcal enteritis may occur after oral or parenteral therapy.<sup>97, 98</sup> More often and less serious, oral or vaginal moniliasis complicates treatment, a complication that may require specific therapy.

### Significant Food and Drug Interactions

Food adversely affects the absorption of tetracycline, chlortetracycline, methacycline, and demeclocycline. Doxycycline and minocycline absorption decreases by less than 20%, which does not appear to be important clinically.<sup>99, 100</sup> All the tetracyclines form complexes with divalent or trivalent cations. Therefore, absorption is markedly decreased when these drugs are administered simultaneously with calcium, magnesium, and aluminum in antacids; milk; iron and iron-containing tonics; multivitamins; didanosine; or sucralfate. Administration of the drugs should be spaced by 2 hours.<sup>101, 102</sup> Sodium bicarbonate also has an adverse effect on absorption and should not be administered simultaneously.<sup>103</sup> Cimetidine has been shown to decrease the absorption of tetracycline, but this is unlikely to be significant in the clinical situation.<sup>104</sup> Carbamazepine (Tegretol), diphenylhydantoin, and barbiturates decrease the normal half-life of doxycycline to almost one half by increasing the hepatic metabolism of the antibiotic.<sup>105, 106</sup> Chronic ethanol ingestion has also resulted in a shorter half-life of doxycycline but not tetracycline, presumably also through the induction of hepatic microsomal enzymes.<sup>107</sup> Methoxyflurane anesthesia may cause nephrotoxicity when administered with tetracyclines.<sup>108</sup> It has been suggested that this adverse interaction occurs with the newer, less nephrotoxic fluorinated anesthetic agents as well.<sup>109</sup> The use of these antibiotics concurrently with diuretics produces an elevated blood urea nitrogen level, although the exact mechanism has not been determined.<sup>110</sup> It has been reported that women receiving oral contraceptives have become pregnant while receiving tetracycline. This may be caused by the reduction in bacterial hydrolysis of conjugated estrogen in the intestine.<sup>111, 112</sup> Women should be advised to use an additional form of birth control. The tetracyclines may potentiate the effects of oral anticoagulants, making careful monitoring of prothrombin times essential.

There is in vitro antagonism when anti-infective agents that are primarily inhibitory are combined with cidal agents. This appears to account for the poor outcome in the treatment of pneumococcal meningitis with penicillin and tetracycline. Whether it can be generalized to other indications is not known.<sup>113</sup>

### Indications

The tetracyclines are the drugs of choice or effective alternative therapy for a wide variety of bacterial, chlamydial, mycoplasmal, and rickettsial infections (Table 24-5).<sup>114-116</sup> The use of minocycline for early (within the first year of disease) rheumatoid arthritis is of note as is the use of intrapleural tetracycline for the control of malignant pleural effusions.<sup>117-119</sup> The tetracyclines have no role in the treatment of viral or fungal diseases. Tetracycline or doxycycline can be used interchangeably for most of these indications. However, compliance may be better with doxycycline since it can be taken

TABLE 24-5 Major Therapeutic Indications for the Tetracyclines\*

| Major Indications                                                                        | Effective Alternative Therapy                                                                                  |
|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| <i>Borrelia burgdorferi</i> (Lyme disease, early)                                        | Acne, severe                                                                                                   |
| <i>Chlamydia recurrentis</i> (relapsing fever)                                           | <i>Actinomyces israelii</i> (actinomycosis)                                                                    |
| <i>Chlamydia trachomatis</i> (with gentamicin in seriously ill patients)                 | Anthrax                                                                                                        |
| <i>Calymmatobacterium granulomatis</i> (granuloma inguinale)                             | <i>Bartonella henselae</i> and <i>quintana</i>                                                                 |
| Chlamydial infections                                                                    | <i>Campylobacter fetus jejuni</i>                                                                              |
| <i>Chlamydia pneumoniae</i> (TWAR strain)                                                | Chronic bronchitis (acute exacerbation)                                                                        |
| Epididymitis, acute (sexually transmitted form)                                          | <i>Clostridium tetani</i>                                                                                      |
| Inclusion conjunctivitis (adult)                                                         | <i>Eikenella corrodens</i>                                                                                     |
| Lymphogranuloma venereum                                                                 | <i>Francisella tularensis</i> (tularemia)                                                                      |
| Ornithosis, psittacosis                                                                  | <i>Legionella</i> spp. (doxycycline ± rifampin)                                                                |
| Trachoma                                                                                 | <i>Leptospira</i> (leptospirosis)                                                                              |
| Urethral, endocervical, or rectal infections in adults                                   | <i>Leptotrichia buccalis</i>                                                                                   |
| Ehrlichia                                                                                | <i>Mycobacterium leprae</i> (minocycline)                                                                      |
| <i>Helicobacter pylori</i> (plus metronidazole plus bismuth subsalicylate)               | <i>Mycobacterium marinum</i> (minocycline)                                                                     |
| Pelvic inflammatory disease (acute, in combination with other antibiotics) (doxycycline) | <i>Mycoplasma pneumoniae</i>                                                                                   |
| <i>Pseudomonas mallei</i> (glanders) (streptomycin with a tetracycline)                  | <i>Nocardia</i> (minocycline)                                                                                  |
| Rickettsial infections (some prefer chloramphenicol for severe infections)               | <i>Pasteurella multocida</i>                                                                                   |
| Q fever                                                                                  | <i>Pseudomonas pseudomallei</i> (meliodosis) (doxycycline with TMP/SMX and chloramphenicol)                    |
| Rickettsial pox                                                                          | Rat-bite fever ( <i>Spirillum minus</i> )                                                                      |
| Rocky Mountain spotted fever                                                             | <i>Streptococcus moniliformis</i>                                                                              |
| Typhus fever                                                                             | <i>Stenotrophomonas maltophilia</i> (minocycline)                                                              |
| Jerethmia, nonspecific                                                                   | <i>Treponema pallidum</i> (syphilis)                                                                           |
| Jerethmia syndrome, acute                                                                | <i>Treponema pertense</i> (yaws, nasopalatal)                                                                  |
| <i>Vibrio cholerae</i> (cholera)                                                         | <i>Ureaplasma urealyticum</i>                                                                                  |
| <i>Vibrio parahaemolyticus</i>                                                           | <i>Yersinia pestis</i> (plague)                                                                                |
| <i>Vibrio vulnificus</i>                                                                 | Alternative Prophylaxis                                                                                        |
|                                                                                          | Oral bowel preparation for intestinal surgery (tetracycline in combination with neomycin or doxycycline alone) |
|                                                                                          | Meningococcal disease prophylaxis (minocycline)                                                                |

\*Unless specified, tetracycline and doxycycline can be considered interchangeable abbreviations: TMP/SMX, Trimethoprim-sulfamethoxazole

## CHLORAMPHENICOL

Soon after chloramphenicol was released in the United States in 1949, reports linked this highly effective agent with aplastic anemia, and it quickly fell into disfavor. The increased awareness of the pathogenicity of anaerobic organisms and the development of ampicillin-resistant *H. influenzae* accounted for a brief resurgence. However, the availability of other agents has dramatically reduced the need for this antibiotic. Because it is effective, readily available (often over the counter), and inexpensive, it is still used as first-line therapy for enteric fever and other infections in many parts of the world. In the United States and other developed nations, chloramphenicol remains a useful antibiotic, but only as alternative therapy in seriously ill patients or for patients infected with very antibiotic-resistant organisms.

## Structure, Derivation, Brand Names, and Preparations

Like the early tetracyclines, chloramphenicol was discovered by screening organisms for their antimicrobial activity. Isolated independently by Burkholder from a mulched field near Caracas, Venezuela<sup>120</sup> and by workers at the University of Illinois from compost,<sup>121</sup> the organism producing the active compound was named *Streptomyces venezuelae*.<sup>122</sup> The structure of chloramphenicol is shown in Figure 24-3. It was the first antibiotic whose chemical synthesis was economically and technically practical for large-scale production.<sup>123</sup> In many countries, chloramphenicol is available in 250-mg capsules (Chloromycetin, Parke-Davis), suspension 150 mg/5 ml (Chloromycetin Palmitate), and as a parenteral formulation (Chloromycetinum Succinate, 1-g powder). Generic formulations are also available. It also is available as Chloromycetin ophthalmic ointment 1%;

Chloromycetin ophthalmic 25 mg (powder to prepare ophthalmic solution) and Chloromycetin Otic (drops). In the United States, Parke-Davis discontinued manufacturing the oral Chloromycetin Kapsals (250 mg) in 1995 and the Chloromycetin Palmitate in 1991. No oral products are currently available in the United States. In March 1998, Parke-Davis sold their remaining line to Monarch Pharmaceuticals (David Rhodes, Medical Affairs, Parke-Davis, personal communication).

Thiamphenicol, not available in the United States, is an analogue in which the *p*-nitro group on the benzene ring is replaced by a methylsulfonyl group. Its spectrum of activity is similar to that of chloramphenicol, but it has not been reported to cause aplastic anemia.

## Mechanism of Action

Chloramphenicol appears to enter the cell by an energy-dependent process.<sup>124</sup> Once within the cell, it inhibits protein synthesis. This is accomplished by reversibly binding to the larger 50-S subunit of the 70-S ribosome at a locus that prevents the attachment of the amino acid-containing end of the aminoacyl-transfer RNA to its binding region. Without this attachment, the association of the amino acid substrate with peptidyltransferase does not occur and peptide bond formation is prevented.<sup>1</sup> This block in protein synthesis produces a static effect against most sensitive microorganisms. However, chloramphenicol is bactericidal against some meningeal pathogens such as *H. influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* but not group B streptococci or enteric gram-negative bacilli at concentrations that can be achieved therapeutically.<sup>125-127</sup> Although mammalian cells contain primarily 80-S ribosomes that are unaffected by chloramphenicol, the mitochondria do contain 70-S particles. The effect of chloramphenicol on these has been suggested as a cause for the dose-related bone marrow suppression of the compound but not the idiosyncratic aplastic anemia.<sup>128</sup>

## In Vitro Activity

Chloramphenicol is extremely active against a variety of organisms, including bacteria, spirochetes, rickettsiae, chlamydiae, and mycoplasmas. The percent of strains of bacteria inhibited at various concentrations of antibiotic is listed in Table 24-6. Most of the gram-positive and gram-negative aerobic bacteria are inhibited by concentrations easily achieved in the serum of patients, but more active or less toxic therapeutic agents are available for most of these pathogens.<sup>9, 10, 16, 24, 123, 129-133</sup> Salmonellae including *Salmonella typhi* are generally susceptible.<sup>134</sup> In the United States, resistant strains occasionally occur,<sup>134</sup> but imported strains may be highly resistant. The three most common organisms causing meningitis in childhood (*H. influenzae*, *Strep. pneumoniae*, and *N. meningitidis*) are highly susceptible,<sup>10, 135, 136</sup> although rare resistant strains of each species have been reported. The overall rate of *H. influenzae* resistance among clinical strains in the United States is approximately 0.6%.<sup>137</sup> Indeed, strains of *H. influenzae* that cause clinical infections and are resistant to both chloramphenicol and ampicillin have been isolated in several parts of the world.<sup>138-140</sup> These resistant isolates are rare in the United States and Canada but rather frequent in Spain.<sup>141, 142</sup> Chloramphenicol is one of the most active antibiotics against anaerobic bacteria including the *B. fragilis* group, but other agents have

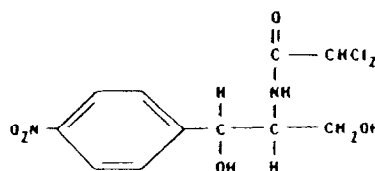


FIGURE 24-3 Chemical structure of chloramphenicol

TABLE 24-6 Activity of Chloramphenicol against Selected Bacteria\*

| Bacteria                                     | No. of Strains | Cumulative Percentage Inhibited at Indicated Concentration (µg/ml) |     |     |     |     |
|----------------------------------------------|----------------|--------------------------------------------------------------------|-----|-----|-----|-----|
|                                              |                | 0.4                                                                | 0.8 | 1.6 | 3.2 | 6.4 |
| Aerobic bacteria                             |                |                                                                    |     |     |     |     |
| Gram-positive                                |                |                                                                    |     |     |     |     |
| <i>Staphylococcus aureus</i>                 | 291            | 0                                                                  | 0   | 0   | 5   | 55  |
| <i>Staph. aureus</i> (methicillin-resistant) | 22             | 0                                                                  | 0   | 0   | 0   | 20  |
| <i>Streptococcus pyogenes</i>                | 303            | 0                                                                  | 0   | 20  | 92  | 99  |
| <i>Streptococci</i> , group B                | 146            | 0                                                                  | 0   | 0   | 85  | 99  |
| <i>Viridans streptococci</i>                 | 193            | 0                                                                  | 0   | 0   | 60  | 90  |
| <i>Enterococci</i>                           | 387            | 0                                                                  | 0   | 0   | 0   | 0   |
| <i>Streptococcus pneumoniae</i>              | 78             | —                                                                  | —   | —   | 50  | 100 |
| Gram-negative                                |                |                                                                    |     |     |     |     |
| <i>Haemophilus influenzae</i>                | 17             | —                                                                  | —   | 50  | 100 | —   |
| <i>Neisseria meningitidis</i>                | 7              | —                                                                  | 50  | —   | 100 | —   |
| <i>Neisseria gonorrhoeae</i>                 | 106            | 5                                                                  | 52  | 97  | 100 | —   |
| <i>Escherichia coli</i>                      | 71             | 0                                                                  | 0   | 5   | 30  | 75  |
| <i>Klebsiella pneumoniae</i>                 | 35             | 0                                                                  | 0   | 6   | 70  | 75  |
| <i>Enterobacter</i>                          | 10             | 0                                                                  | 0   | 0   | 10  | 20  |
| <i>Serratia marcescens</i>                   | 111            | 0                                                                  | 0   | 0   | 5   | —   |
| <i>Proteus mirabilis</i>                     | 209            | 0                                                                  | 0   | 0   | 20  | 60  |
| <i>Proteus</i> (indole-positive)             | 32             | 0                                                                  | 0   | 0   | 10  | 40  |
| <i>Salmonella typhi</i>                      | 81             | 0                                                                  | 0   | 0   | 50  | 95  |
| <i>S. paratyphi</i> A                        | 31             | —                                                                  | —   | —   | 28  | 97  |
| <i>Shigella</i> spp                          | 44             | —                                                                  | 20  | 30  | 75  | 90  |
| <i>Vibrio cholerae</i>                       | 64             | —                                                                  | —   | —   | —   | 84  |
| <i>Brucella</i> spp                          | 25             | 0                                                                  | 0   | 28  | 92  | 100 |
| <i>Pseudomonas aeruginosa</i>                | 11             | 0                                                                  | 0   | 0   | 0   | 0   |
| <i>P. pseudomallei</i>                       | 10             | 0                                                                  | 0   | 0   | 0   | 50  |
| <i>Bordetella pertussis</i>                  | 31             | 20                                                                 | 45  | 85  | 97  | 99  |
| Anaerobic bacteria                           |                |                                                                    |     |     |     |     |
| Gram-positive                                |                |                                                                    |     |     |     |     |
| <i>Peptococcus</i> spp                       | 145            | 8                                                                  | 25  | 67  | 97  | 98  |
| <i>Peptostreptococcus</i> spp.               | 72             | 11                                                                 | 37  | 63  | 96  | 100 |
| <i>Propionibacterium acnes</i>               | 16             | 12                                                                 | 31  | 94  | 100 | —   |
| <i>Eubacterium lentum</i>                    | 14             | 14                                                                 | 14  | 28  | 71  | 100 |
| <i>Clostridium perfringens</i>               | 34             | 0                                                                  | 0   | 15  | 100 | —   |
| <i>Clostridium</i> spp.                      | 17             | 12                                                                 | 12  | 53  | 88  | 100 |
| Gram-negative                                |                |                                                                    |     |     |     |     |
| <i>Veillonella</i> spp                       | 13             | 23                                                                 | 46  | 85  | 100 | —   |
| <i>Bacteroides fragilis</i>                  | 195            | 0                                                                  | 1   | 2   | 23  | 98  |
| <i>Prevotella melaninogenica</i>             | 29             | 14                                                                 | 31  | 93  | 96  | 100 |
| <i>Fusobacterium</i> spp                     | 18             | 39                                                                 | 44  | 56  | 89  | 100 |

\*The National Committee for Laboratory Standards recommends that 8 µg/ml or less be considered susceptible, 16 µg/ml intermediate and 32 µg/ml or greater be considered resistant. For *Haemophilus* ≥ 2 µg/ml are sensitive, 4 µg/ml intermediate and ≥ 8 µg/ml resistant. For testing *S. pneumoniae* the breakpoints are ≤ 4, 8, and ≥ 16 µg/ml.<sup>1</sup>

Data from refs. 8-10, 12, 30, 123 and 129-147

become more important clinically to treat infections caused by these bacteria.<sup>24, 144-147</sup>

Bacteria develop resistance to chloramphenicol by becoming impermeable to the drug or by producing an enzyme, acetyltransferase, that acetylates the antibiotic to an inactive diacetyl derivative.<sup>148, 149</sup> This latter mechanism has been R factor mediated and has been responsible for widespread epidemics of chloramphenicol-resistant typhoid fever and *Shigella* dysentery in Central and South America, Vietnam, India, and other countries.<sup>150-153</sup> It has been suggested that the unrestricted over-the-counter sales of chloramphenicol in the countries involved may be an important factor that provides antibiotic pressure for the development of these resistant strains.<sup>152, 153</sup> In the United States, chloramphenicol resistance in *Salmonella* has been traced to the use of chloramphenicol on dairy farms.<sup>16</sup>

### Pharmacology

Chloramphenicol serum levels achieved by different routes of administration and with different product forms are listed in Figure 24-4. Chloramphenicol in the encapsulated form is well absorbed from the gastrointestinal tract and results in peak serum levels of 12 µg/ml of active antibiotic after a 1-g dose.<sup>154, 155</sup> Since it is a very bitter substance, aqueous solutions may not be accepted by children. A tasteless suspension in the form of chloramphenicol palmitate is available in some countries. This preparation must be hydrolyzed in the intestine to produce active chloramphenicol. Although earlier

formulations sometimes produced erratic serum levels, the bioavailability of chloramphenicol palmitate in the current formulation is the same as in the capsules and is effective for children with *H. influenzae* meningitis (A. J. Glazko, Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Ann Arbor, Michigan, personal communication).<sup>156, 157</sup> In the United States, the oral preparations are no longer available. Practitioners must resort to using the intravenous preparation orally; pharmacokinetic data is meager. In one patient receiving an oral dose equivalent to 1 g of chloramphenicol mono succinate diluted in a glass of milk, peak serum levels at 2 hours were 4.3 µg/ml by microbiologic assay compared with 5.0 µg/ml in three volunteers receiving the compound intravenously and assayed by the same methodology. If oral therapy is required using this intravenous formulation, assays are essential.<sup>158</sup>

The intravenous preparation of the drug is the soluble but inactive chloramphenicol succinate ester that is rapidly hydrolyzed within the body to biologically active chloramphenicol.<sup>159</sup> This preparation produces active chloramphenicol levels in the serum that are 70% of those obtained after oral administration due to incomplete hydrolysis.<sup>154</sup> Bhutta and colleagues found consistently lower serum levels when treating typhoid fever compared with other diseases with intravenous chloramphenicol in children and suggested a dose of 75 mg/kg/day instead of 50 mg/kg/day to compensate.<sup>160</sup> Intramuscular injection is well tolerated and in most studies produces peak serum levels and areas under the serum-level curve similar to those of intravenous administration.<sup>161-164</sup> In adults with enteric fever, how-

intermediates of the antibiotic. This type of toxicity has occurred in identical twins, which suggests a genetic predisposition.<sup>191</sup> Morley and coworkers have observed that mice given chloramphenicol after treatment with busulfan had a progressive decrease in the number of pluripotential stem cells, whereas control mice did not,<sup>195</sup> suggesting that the aplastic anemia might result in patients with unrecognized preexisting residual marrow damage either genetic or acquired. In 1967, Holt observed that the aplastic anemia occurred only after oral administration of the antibiotic.<sup>196</sup> He postulated that the fatal reaction may be caused by the absorption of toxic products produced by enzymatic degradation of chloramphenicol, perhaps as a result of specific types of bacteria colonizing the gut of affected people. Supporting this hypothesis, Jimenez and colleagues have shown that one of chloramphenicol's metabolites, dehydrochloramphenicol, is 10- to 20-fold more cytotoxic than chloramphenicol yet is only one third as effective in inhibiting protein synthesis,<sup>197</sup> thus suggesting that this metabolite and perhaps others may play a significant role in this toxicity. These toxic metabolites may undergo further metabolic transformation in the bone marrow with on-site production of toxic intermediates.<sup>198-199</sup> Although the number of cases reported is greater after oral therapy, a number of cases of aplastic anemia from parenteral chloramphenicol even after the administration of eyedrops have also been reported.<sup>200-201</sup> These latter cases have received considerable debate but are very rare; estimates of serious hematologic toxicity appear to be no more than 3 in 442,543 patients and most likely much less.<sup>202-203</sup> In a review of 426 cases of aplastic anemia, none of the patients used chloramphenicol eye drops.<sup>204</sup>

Although most cases of aplastic anemia from chloramphenicol become apparent after the completion of therapy, it should be emphasized that 22% of the cases occur concurrently with antibiotic administration.<sup>192, 201</sup> Whether some of these episodes can be prevented by checking the blood counts of patients is not known. Until the pathogenesis of the toxicity is clearly understood, it is recommended that a complete blood count be obtained on a twice-a-week basis from all patients receiving chloramphenicol. If the white blood cell count decreases below 2500/mm<sup>3</sup>, it is desirable to discontinue treatment with the antibiotic if the clinical condition allows. It should be recognized, however, that low numbers of white blood cells may occur in illnesses for which chloramphenicol is used, such as typhoid fever.

Also of concern are the reports of childhood leukemia after the use of chloramphenicol. Although these cases generally follow the aplastic anemia, a population-based case-control interview study of 309 childhood leukemia cases and 618 age- and sex-matched controls showed a significant dose-response relation between chloramphenicol and the risk of both acute lymphocytic and nonlymphocytic leukemia, particularly after treatment for greater than 10 days in children without prior aplastic anemia. Until this is more clearly defined, it seems prudent to change therapy as quickly as possible to alternate agents when organisms prove susceptible to other equally effective and less toxic antibiotics.<sup>205</sup>

Chloramphenicol may also produce a hemolytic anemia in patients with the Mediterranean form of glucose-6-phosphate dehydrogenase deficiency. This apparently does not occur with the milder A type glucose-6-phosphate dehydrogenase deficiency, which is the most common form in blacks.<sup>206</sup>

### Gray Baby Syndrome

The gray baby syndrome of neonates is characterized by abdominal distention, vomiting, flaccidity, cyanosis, circulatory collapse, and death. The side effect results from a diminished ability of neonates to conjugate chloramphenicol and to excrete the active form in the urine.<sup>207</sup> If chloramphenicol is necessary in premature infants and neonates, the dose should be reduced to 25 mg/kg/day and the antibiotic levels should be monitored. This syndrome has also been recognized in toddlers and after accidental overdoses in adults.<sup>208-209</sup>

col of greater than 50 µg/ml and may present with unexplained metabolic acidosis.<sup>210</sup> Large-volume exchange transfusions or charcoal hemoperfusion have been used to accelerate drug removal. This syndrome is due in part to impaired myocardial contractility related to direct interference of myocardial tissue respiration and oxidative phosphorylation.<sup>211-214</sup>

### Optic Neuritis

Optic neuritis resulting in decreased visual acuity has been described in patients receiving prolonged chloramphenicol therapy.<sup>215</sup> The symptoms are generally reversible, but loss of vision has occurred. Other neurologic sequelae such as peripheral neuritis, headache, depression, ophthalmoplegia, and mental confusion have also been described.

### Other Types

Hypersensitivity reactions (including rashes and drug fevers) and anaphylaxis are rare. Herxheimer-like responses during therapy for syphilis, brucellosis, and typhoid fever have been observed. Symptoms involving the gastrointestinal tract, including nausea, vomiting and diarrhea, glossitis, and stomatitis, occur but have not been a major problem. Bleeding due to decreased vitamin K synthesis has resulted from prolonged administration.

### Significant Drug Interactions

Chloramphenicol prolongs the half-life of tolbutamide, chlorpropamide, phenytoin, cyclophosphamide, and warfarin (Coumadin), apparently by inhibiting hepatic microsomal enzymes.<sup>216-219</sup> Severe toxicity and death have occurred. Phenytoin, rifampin, and phenobarbital have been observed to decrease the serum concentration and increase the total body clearance of chloramphenicol, perhaps by inducing hepatic microsomal enzymes. Serum concentrations should be monitored when these drugs are administered concurrently.<sup>220-221</sup> The physician should be on the alert for toxicity from other agents that

TABLE 24-7 Indications for Chloramphenicol\*

| Indications                                          | Comments                                                                                              |
|------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Therapy of Choice</b>                             |                                                                                                       |
| None†                                                |                                                                                                       |
| <b>Effective Alternative Therapy</b>                 |                                                                                                       |
| Bacterial meningitis                                 | For penicillin-allergic patients                                                                      |
| <i>Haemophilus influenzae</i>                        |                                                                                                       |
| <i>Streptococcus pneumoniae</i>                      |                                                                                                       |
| <i>Neisseria meningitidis</i>                        |                                                                                                       |
| Brain abscess                                        |                                                                                                       |
| <i>Chlamydia psittaci</i> (psittacosis)              |                                                                                                       |
| <i>Clostridium perfringens</i>                       |                                                                                                       |
| Ehrlichiosis                                         |                                                                                                       |
| Rickettsial infections                               | Preferred by some when patients require parenteral therapy, during pregnancy, and for young children  |
| Rocky Mountain spotted fever                         |                                                                                                       |
| Typhus (murine)                                      |                                                                                                       |
| Scrub typhus                                         |                                                                                                       |
| Tick-bite fever                                      |                                                                                                       |
| Q fever                                              |                                                                                                       |
| <i>Pseudomonas mallei</i>                            | Used with streptomycin                                                                                |
| <i>Pseudomonas pseudomallei</i> (melioidosis, acute) | Used with doxycycline                                                                                 |
| Typhoid fever and invasive salmonellosis             | Strains in some areas may be chloramphenicol-resistant, not used for gastroenteritis or carrier state |
| <i>Vibrio vulnificus</i> cellulitis and/or sepsis    |                                                                                                       |
| <i>Yersinia pestis</i>                               |                                                                                                       |

\*The usual recommended adult dose is 50 mg/kg/day. Some prefer 75 mg/kg/day for the treatment of typhoid fever. For infections of the central nervous system, 100 mg/kg/day is suggested. See text.

metabolized by the liver when administering this agent and monitor serum levels when these drugs are administered recently. Chloramphenicol may delay the response of anemias, folic acid, and vitamin B<sub>12</sub>.<sup>122</sup>

Chloramphenicol is primarily a bacteriostatic agent and will antagonize in vitro the bactericidal activity of the penicillins, cephalosporins, and aminoglycoside antibiotics. This has doubtful clinical relevance in most instances. However, care should be exercised in the use of such combinations for infections that require bactericidal therapy for efficacy such as for infections in the granulocytopenic host or in the treatment of endocarditis.<sup>123</sup> In the treatment of meningitis the bacteriostatic activity of chloramphenicol against group B streptococci and its in vitro antagonism with ampicillin against this organism are of concern and should be considered in selecting therapy when this organism is likely to be a pathogen.<sup>127</sup>

## Indications

Clinical indications for the use of chloramphenicol are listed in Table 24-7. With the possible exception of typhoid fever in areas where cost and availability make it the primary therapy, it is no longer the drug of choice for any specific infection. The third-generation cephalosporins have superseded chloramphenicol for the treatment of bacterial meningitis in infants and children, though chloramphenicol is still used for the treatment of meningitis in the penicillin-allergic patients.<sup>124</sup> Occasionally, the antibiotic is useful in the differential diagnosis includes both meningococcemia and Rocky Mountain spotted fever, diseases that may be difficult to distinguish on clinical characteristics. Of note is the occasional use of chloramphenicol for the treatment of infections caused by multiply resistant organisms, although its use for meningitis caused by penicillin-resistant pneumococcus has been discouraging.<sup>124-128</sup>

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## MECHANISM OF ACTION

The rifamycins exert a bactericidal effect by inhibition of DNA dependent RNA polymerase at the  $\beta$ -subunit, which prevents chain initiation but not elongation.<sup>4</sup> Mammalian mitochondrial RNA synthesis is not impaired at clinically achievable concentrations.

## PHARMACOLOGY

Rifampin is available in the United States as a capsule of orange-red powder and as a solution for intravenous infusion. The oral preparation is almost completely absorbed from the gastrointestinal tract to yield peak plasma concentrations of approximately 7 to 10  $\mu\text{g/ml}$  (range, 4 to 32) within 1 to 4 hours after the ingestion of 600 mg in adults or 10 mg/kg of body weight in children. Higher doses such as 1200 mg in adults result in a similar, more-than-proportional increase in the peak ( $\geq 30 \mu\text{g/ml}$ ) serum concentration, because such doses exceed the biliary transport maximum ( $T_m$ ) for the excretion of rifampin.<sup>5</sup> The area under the curve shows a similar, more-than-proportional increase after saturation of the biliary  $T_m$ , which usually occurs with doses between 300 and 450 mg. For this reason, a single daily dose 450 mg or greater results in higher area-under-the-curve values for rifampin than do divided doses totaling the same amount.

The recommended dosage is usually 10 to 20 mg/kg (600 mg maximum) in a single daily administration. A 1% weight/volume oral suspension containing 10 mg/ml may be prepared by mixing the contents of four 300-mg capsules with 120 ml of any of several commercially available syrups according to the directions in the package insert or the *Physicians' Desk Reference*.<sup>6</sup> It should not be cosuspended with other antituberculosis agents such as isoniazid or pyrazinamide, or with ascorbic acid, because such cosuspensions are associated with a significant decline in detectable concentrations of the drugs.<sup>7</sup> Fixed-dose combinations with isoniazid or pyrazinamide, or both, in a capsule or tablet have not resulted in impaired absorption, however, and can be used to prevent ill-advised monotherapy of tuberculosis.<sup>8</sup> An oral desensitization protocol for rifampin was adapted from one devised for penicillin and used successfully in treating patients with previous cutaneous hypersensitivity reactions to rifampin.<sup>9</sup>

Dosage adjustment is unnecessary in renal failure, but rifampin should be avoided or used with caution (perhaps at a lower dosage) in patients with hepatic dysfunction. Food with a high fat concentration interferes with absorption, lowering and delaying peak blood levels.<sup>10</sup> Para-aminosalicylic acid also interferes with absorption. In one study, absorption was found to be diminished in patients with acquired immunodeficiency syndrome (AIDS) and D-xylose malabsorption.<sup>11</sup>

The drug is 80% protein bound in serum and distributes into a volume calculated to be 160% of body weight. Plasma clearance is through hepatic uptake, deacetylation to an active metabolite, and biliary excretion. Deacetylation diminishes reabsorption and increases fecal excretion, but there is significant enterohepatic circula-

## Chapter 25

### Rifamycins

BARRY M. FARR

Rifampin is a semisynthetic derivative of rifamycin B, a macrocyclic antibiotic compound produced by the mold *Streptomyces mediterranei*. First isolated from fermentation culture of a soil isolate in 1957, rifamycins were named for a then-current French movie, *Rififi*.<sup>1</sup> Rifampin, which is the 3,4-methylpiperazinyliminomethyl derivative of rifamycin SV, is more soluble and active in vitro than is its parent compound (Fig. 25-1).<sup>2</sup> Rifampin is a zwitterion (inner salt) that is soluble in acidic aqueous solution, is even more solu-

